REMARKS

In response to the Office Action mailed April 26, 2006, Applicants have amended claims 1, 4, 12 and canceled claim 13. It is urged that support for all the above amendments may be found throughout the specification as originally filed, for example at page 121, lines 15-18. No new matter has been added. The above amendments are not to be construed as acquiescence with regard to the Examiner's rejections and are made without prejudice to prosecution of any subject matter removed or modified by this amendment in a related divisional, continuation or continuation-in-part application. Following the amendments, claims 1, 3, 4, 11 and 12 are pending in the application. Favorable reconsideration of the subject application is respectfully requested in view of the above amendments and the following remarks.

Claim rejections under 35 U.S.C. § 112, second paragraph

Claims 1, 3, 4 and 11-13 stand rejected under 35 U.S.C. § 112, second paragraph as allegedly indefinite. The Action contends that the phrase "at least 20 contiguous residues of a sequence" is indefinite since the word "residues" usually refers to amino acids and not nucleic acids. The Action further alleges that claims 12 and 13 omit essential steps. The Action contends that Claim 12 omits the step of whether the polynucleotide is expressed, whether sufficient amount of the gene product is produced so as to stimulate an immune response and whether the polynucleotide stimulates an immune response. Claim 13 allegedly omits the steps of whether the polynucleotide is expressed and whether sufficient amount of the gene product is produced so as to treat lung cancer.

Applicants respectfully traverse the rejection and submit that the claimed subject matter would be immediately clear to the skilled artisan. In particular, Applicants note that a quick search using Google shows that the use of the term "residue" in reference to nucleic acids is quite common. Accordingly, Applicants submit that the use of the word "residue" in reference to nucleic acids would be clearly understood by the skilled artisan. Notwithstanding these remarks, Applicants have amended claim 1 to remove reference to "20 contiguous residues." Further, without acquiescing to the rejections and without prejudice to prosecution of such

subject matter in a related application, Applicants have canceled claim 13 and amended claim 12 to recite "administering to the patient a suitable dose of the composition of claim 11, thereby stimulating an immune response in the patient." Accordingly, Applicants submit that the rejection has been obviated and may be properly withdrawn.

Claim rejections under 35 U.S.C. § 112, first paragraph (written description)

Claims 1, 3, 4, and 11-13 stand rejected under 35 U.S.C. § 112, first paragraph as allegedly failing to comply with the written description requirement. In particular, the Action contends that the specification only discloses the polynucleotide sequence of SEQ ID NO:160, encoding the amino acid sequence of SEQ ID NO:161 while the claims allegedly encompass sequences including unknown nucleotide sequence at the 5' and 3' ends and/or within the sequence, as well as encompassing a genus of numerous structural variants, none of which is supported by the specification. The Action further contends that the scope of the claims includes unknown and unidentified genes that either encode or do not encode a polypeptide and that no function could be ascribed to the polypeptide of SEQ ID NO:161.

Applicants respectfully traverse the rejection on the following grounds. As an initial matter, without acquiescing to the stated grounds for rejection, and without prejudice to prosecution of such subject matter in a related application, Applicants have amended claim 1 to remove recitation of fragments, polynucleotide variants that hybridize and variants having 75%-90% identity to the polynucleotide of SEQ ID NO:160. Claim 1 has been further amended to include the limitation "wherein the degenerate variants encode the polypeptide provided in SEQ ID NO:161."

Applicants were the first to describe the full-length polynucleotide set forth in SEQ ID NO:160 and its expression in lung cancer. Furthermore, the claim specifically recites an "isolated polynucleotide" comprising SEQ ID NO:160. The specification clearly defines this at page 52, lines 10-16 as follows:

> "Isolated," as used herein, means that a polynucleotide is substantially away from other coding sequences, and that the DNA molecule does not contain large portions of unrelated coding DNA, such as large chromosomal fragments or other functional genes or polypeptide coding regions. Of course, this refers to the DNA

molecule as originally isolated, and does not exclude genes or coding regions later added to the segment by the hand of man.

Thus, whether additional sequence may or may not be added to the isolated sequence of SEQ ID NO:160, Applicants submit that they are entitled to isolated polynucleotides that comprise the sequence set forth in SEQ ID NO:160, the complement thereof and degenerate variants thereof, and that the skilled artisan would readily appreciate that Applicants were in possession of the claimed subject matter upon review of the instant disclosure.

Concerning the Action's allegation at page 5 that the scope of the claims includes unknown and unidentified genes that either encode or do not encode a polypeptide, Applicants submit that the claims are directed to polynucleotides and not polypeptides. Further, methods using the polynucleotide to generate an immune response against a polypeptide encoded by the claimed polynucleotides or for the treatment of lung cancer in no way rely on the biological function of the polypeptide. Accordingly, Applicants submit that the biological function of the polypeptide is not relevant.

In view of the above remarks and amendments, Applicants submit that the claimed invention satisfies the written description requirement under 35 U.S.C. § 112, first paragraph and respectfully request reconsideration and withdrawal of the rejection.

Claim rejections under 35 U.S.C. § 112, first paragraph (enablement)

Claims 1, 3, 4, and 11-13 stand rejected under 35 U.S.C. § 112, first paragraph on the basis that the specification, while being enabling for a polynucleotide sequence comprising SEQ ID NO:160, allegedly does not reasonably provide enablement for fragments and variants thereof or the use of such polynucleotides for generating an immune response or for the treatment of lung cancer. The Action also goes on at length to allege that the specification fails to provide the biological function of a polypeptide comprising the amino acid sequence of SEQ ID NO:161 and fails to provide adequate guidance for how to use such a polypeptide. Further, the Action contends that claim 4 reads on a host cell transfected or transformed *in vivo* and that claims 12 and 13 read on gene therapy for stimulating an immune response and treating a lung cancer *in vivo*. Finally, in support of the contention that the claims are not enabled, the Examiner

cites a number of references, allegedly disclosing problems with gene therapy. As such, the Action concludes that the claims lack enablement.

Applicants respectfully traverse the rejection on the following grounds.

As an initial note, Applicants note that claim 1 has been amended to remove recitation of fragments, polynucleotide variants that hybridize and variants having 75%-90% identity to the polynucleotide of SEQ ID NO:160. Concerning degenerate variants, Applicants have amended claim 1 to include the limitation "wherein the degenerate variants encode the polypeptide provided in SEQ ID NO:161". Applicants submit that the skilled artisan would readily appreciate how to make and use the claimed degenerate variants in view of general teachings in the art and the teachings of the instant specification, for example, at page 5, lines 3-5 and Table 1 at page 42. Claim 4 has been amended to recite "an isolated" host cell. Claim 13 has been canceled. These amendments are made without acquiescence to the grounds for rejection and without prejudice to prosecution of any subject matter in a related application.

The thrust of the Action's assertions appears to be that the specification does not enable the use of the claimed methods due to a lack of evidence regarding their human implementation. If this is true, the Action is asserting that the claimed invention lacks *in vivo* utility. Although this rejection is not made under 35 U.S.C. § 101, the legal standard to be applied is the same. *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995) (although the Examiner has made the rejection based on § 112, a § 101 rejection for lack of utility would also have been proper.) (See also "Legal Analysis Supporting Utility Examination Guidelines," 60 F.R. 36263, July 14, 1995.)

Applicants respectfully submit that this rejection is improper in view of the PTO Guidelines. In *no* case has a Federal court required an applicant to support an asserted utility with data from human clinical trials. Moreover, in *In re Brana*, the Federal Circuit emphatically rejected the PTO position that human clinical testing is necessary to establish practical utility for an antitumor agent. 51 F.3d 1560. Importantly, the court noted, citing *In re Krimmel*, 130 U.S.P.Q. 205 (C.C.P.A. 1961):

> We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has

> made a significant and useful contribution to the art, **even though it may eventually appear that the compound is without value in the treatment of humans**. (Emphasis added.)

Here, the situation is analogous. Applicants submit that the specification clearly shows that the claimed polynucleotide of SEQ ID NO:160 is overexpressed in ¾ lung squamous tumors and 4/4 head and neck tumors (see Example 3, page 151, lines 17-20). Example 6 further demonstrates the lung tumor-associated expression of this antigen using immunohistochemical staining (see page 156, lines 4-7). Additionally, the specification shows that antibodies against the L762P lung tumor antigen were present in effusion fluid or sera of lung cancer patients but not in normal donors (see Example 16, pages 173-174) suggesting that this self protein can elicit an immune response *in vivo*. Further, Applicants direct the Examiner to Examples 47 and 48 (pages 238-240) that clearly show that mice injected with the L762P-expressing cell line form three times as many lung tumor foci as mice injected with the parent 343T (non-L762P expressing) cell line. These examples further demonstrate methods for transducing and expressing the claimed polynucleotide using viral vectors, methods known in the art and also described in the specification at pages 77-80 and page 100, line 15-page 104, line 19. Additionally, as noted above, the biological function of the polypeptide of SEQ ID NO:161 is not relevant for its use to generate an immune response. See, for example, Example 8 of the instant specification where peptides of SEQ ID NO:161 are used to generate L762P-specific CD4+ T cells.

Concerning the references cited by the Action to support the lack of enablement, while these references represent sweeping generalizations of gene therapy, these references only tell one side of the story. In this regard, to date there are dozens of clinical trials in the U.S., and many more around the world, that involve the use of gene therapy. It is wholly unfair to focus solely upon the technical hurdles faced by some in the field while ignoring the successes.

For example, Applicants draw the Examiner's attention to the results of gene therapy to treat severe combined immunodeficiency. Blaese *et al.*, *Science 270*:475-480 (1995). In this study, two children with a genetic defect in production of adenosine deaminase (ADA) were treated with a cloned ADA gene inserted into a retroviral vector. Both patients continue to display significant improvement in their immune system function. The results of this gene

therapy treatment were markedly superior to those produced earlier by alternative treatment means.

In a cancer context, Roth *et al.*, *Nature Medicine* 2(9):985-991 (1996), have shown that a recombinant retroviral vector targets tumor cells *in vivo*. Moreover, this vector, which encodes the tumor suppresser p53, provided a sufficient level of p53 expression such that apoptosis, or programmed cell death, was triggered in these cells. Accordingly, retrovirus gene therapy was accomplished *in vivo*.

Furthermore, the successes of gene therapy are in no way limited to only these examples. According to a 1995 review article,

> Probably the most remarkable conclusion drawn from the human trials is that human gene transfer is indeed feasible ... [and] most studies have shown that genes can be transferred to humans whether the strategy is *ex vivo* or *in vivo*, and **that all vector types function as intended.** Taken together, the evidence is overwhelming, with successful human gene transfer having been demonstrated in 28 *ex vivo* and 10 *in vivo* studies. Crystal, *Science 270*:404, 405 (1995) (Emphasis added).

Moreover, as shown by an article in the Los Angeles Times of August 28, 2006, scientists are optimistic, despite setbacks since 1995, that gene therapy will help fight serious diseases,

> In recent years, European scientists have cured more than two dozen patients suffering from three rare, and in some cases lethal, immune disorders. Spurred by this success, plus the development of new techniques aimed at making the therapy safer and more effective, more than 300 gene therapy trials, including the one for Parkinson's at U.C. San Francisco, are underway in the U.S. and abroad. (Linda Marsa, "Biotech's Bright Hope," LA Times, August 28, 2006)

Accordingly, gene therapy as a whole clearly evidences enablement and Applicants have demonstrated that the claimed polynucleotide is overexpressed in lung tumor and can be used to generate an immune response. In view of the above remarks and amendments, Applicants respectfully submit that the rejection of the claims under 35 U.S.C.

§ 112, first paragraph, has been obviated and request that the Examiner withdraw this ground of rejection.

Claim rejections under 35 U.S.C. § 102(e)

Claims 1, 3, 4, and 11 stand rejected under 35 U.S.C. § 102(e) as allegedly anticipated by Pauli *et al.*, U.S. Patent No. 6, 309,857 ('857). In particular, the Action contends that Pauli *et al.* discloses the nucleotide sequence of SEQ ID NO:31 which is 99.8% identical to nucleotides 1-2938 of SEQ ID NO:160. Pauli *et al.* further discloses vectors comprising this sequence and host cells comprising said vector. Since this sequence would comprise at least 20 contiguous nucleotides of SEQ ID NO:160, would hybridize to the sequence of SEQ ID NO:160 under highly stringent conditions and buffers containing the sequence would be considered physiologically acceptable, the Action concludes that the claims are anticipated by this reference.

Without acquiescing to the stated grounds for rejection, and without prejudice to prosecution of such subject matter in a related application, Applicants have amended claim 1 to remove recitation of fragments, polynucleotide variants that hybridize and variants having 75%-90% identity to the polynucleotide of SEQ ID NO:160. Further, claim 1 has been amended to include the limitation "wherein the degenerate variants encode the polypeptide provided in SEQ ID NO:161." This limitation necessarily excludes the sequence of Pauli *et al.* since the polynucleotide sequence of SEQ ID NO:31 of Pauli *et al.* does not encode the polypeptide of SEQ ID NO:161. Accordingly, Applicants submit that the rejection has been obviated and may be properly be withdrawn.

Claim rejections under 35 U.S.C. § 102(a)

Claims 1, 3 and 11 stand rejected under 35 U.S.C. § 102(a) as allegedly anticipated by two different EST sequences disclosed by Hillier *et al.* (Accession Nos. AA429919 and AA160879).

Without acquiescing to the stated grounds for rejection, and without prejudice to prosecution of such subject matter in a related application, Applicants have amended claim 1 to remove recitation of fragments comprising at least 20 contiguous nucleotides of SEQ ID NO:160, polynucleotide variants that hybridize and variants having 75%-90% identity to the

polynucleotide of SEQ ID NO:160. As such, Applicants submit that the rejection has been obviated. Reconsideration and withdrawal is respectfully requested.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Applicants respectfully submit that all of the claims remaining in the application are now believed to be in condition for allowance. Favorable consideration and a Notice of Allowance are earnestly solicited.

Respectfully submitted,

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